REMARKS

Claims 1-14 are all the claims pending in the application.

New claims 15-17 are fully supported by the specification. The compound recited in claims 15-17 is "compound 302" found at page 72 of the specification, and encompassed within the compounds recited in claim 6.

No new matter has been added. Entry of the Amendment is respectfully requested.

I. Restriction/Election

At page 2 of the Office Action, the Examiner states that the claims are not drawn to the same scope. The Examiner explains that compounds, corresponding compositions, a method of use and a process of making that are of the same scope are properly considered to form a single inventive concept. Thus, claims corresponding to different categories of different scope lack unity of invention.

In particular, the Examiner points to the scope of the compounds encompassed by claim 1, and states that it is not the same as the scope of claim 5. The Examiner states that Applicants need to limit the scope of the compounds in the method of use claims to that of the compound claims.

In response, Applicants include herewith an amendment to the claims such that each of the method claims (claims 1-4) has been cancelled, and filed in a divisional application. Applicants assert that each of the remaining claims is of the same scope, and therefore respectfully request reconsideration and withdrawal of the objection.

II. Rejection of Claims Under 37 C.F.R. §112

At page 2 of the Office Action, the Examiner rejects claims 1-14 under 35 U.S.C. §112, second paragraph, as being indefinite for the following reasons.

A. The Examiner states that the phrase "hydroxyformamidine derivative" indicates more than the compound being claimed. The Examiner suggests that use of the term "compound" be used in place of "derivative."

In response, Applicants thank the Examiner for the help suggestion and include herewith amendments to the claims such that each occurrence of the term "hydroxyformamidine derivative" has been amended to read "hydroxyformamidine compound."

B. The Examiner states that it is unclear where or why the production of hydroxyeicosatetraenoic acid is inhibited, and whether the inhibition takes place *in vitro* or *in vivo*, and whether the inhibition takes place in everyone. The Examiner requires clarification.

In response, Applicants note the following concerning the inhibition of 20-hydroxyeicosatetraenoic acid (20-HETE) production. For the Examiner's convenience, copies of each of the publications cited below are included with this amendment.

Arachidonic acid can be metabolized by cytochrome P450 (CYP) to 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE; Harder et al., J. Vasc. Res. 32:79-92, 1995). In the rat kidney microsomes, there are three different CYP4A isozymes that can catalyze the omega-hydroxylation of arachidonic acid to 20-HETE, namely CYP4A1, CYP4A2 and CYP4A3 (Ito et al., Am. J. Physiol. 274:F395-404, 1998). In the present Experimental Examples, Applicants used renal microsomes from spontaneously hypertensive rats to examine the effects of Applicants' compounds on the activity of 20-HETE synthesizing enzymes, assayed by detecting

conversion of radio-labeled arachidonic acid to 20-HETE. These experiments were carried out under *in vitro* conditions.

Concerning the mechanism of Applicants' compounds on the inhibition of 20-HETE synthesizing enzymes, Applicants consider that the compounds may bind to heme-binding site of CYP4A instead of arachidonic acid, and thus exhibit inhibitory effects on 20-HETE synthesis.

Because of the specific nature of the compounds of the present application, Applicants consider that the compound could be used in both *in vitro* and *in vivo* methods, and that the methods could be used to treat any patient in need of having production of 20-HETE synthesis blocked.

In view of these comments, Applicants assert that it is clear where, why and how the production of hydroxyeicosatetraenoic acid is inhibited, and thus the claims are definite as written. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

C. The Examiner states that in claims 4, 12 and 14 it is unclear which kidney disease, which cerebrovascular disease and which circulatory disease is being treated. The Examiner further states that the cited diseases embrace unrelated diseases, which have different causes and different treatments. The Examiner requires clarification.

In response, Applicants note the following concerning the relationship between the three disease conditions recited in the claims, and the inhibition of 20-HETE.

Kidney diseases:

It is well-known that 20-HETE can be produced from arachidonic acid by CYP 450 4 isoforms in rat (Ito et al., Am. J. Physiol. 274: F395-404, 1998) and human kidney (Lasker et al.,

J. Biol. Chem., 275: 4118-4126, 2000). 20-HETE has a potent vasoconstrictor activity in intrarenal artery of the rat (Alonso-Galicia et al., Am. J. Physiol. 277: F790-796, 1999) and the dog (Ma et al., Circ. Res. 72:126-136 1993). Renal vasoconstriction is thought to be a risk for the kidneys because reduced renal blood flow causes ischemic conditions, tubular and glomerular damages, and hypertension. Blockade of 20-HETE synthetic pathway would be benefit to kidney diseases including drug-induced renal damage, renal ischemia reperfusion injury, acute renal failure, chronic nephritis, diabetic nephropathy, chronic renal failure, polycystic kidney disease, renal fibrosis, hepatorenal syndrome and renal hypertension. As a matter of fact, CYP4A (20-HETE synthesizing enzyme) expression in kidney was increased in cyclosporin-induced nephrotoxicity model (Nakamura et al., Biochem. Pharmacol. 48: 1743-1746, 1994), streptozotocin induced diabetic rats (Imaoka et al., Biochem. Biophys. Res. Comm. 152: 680-687, 1988), cisplatin-induced nephrotoxicity (Nakamura et al., Res. Comm. Mol. Pathol. Pharmacol. 99:23-32, 1998). The renal excretion of 20-HETE is elevated in hepatorenal syndrome (Sacerdoti et al., J. Clin. Invest., 100: 1264-1270, 1997). From the above-mentioned reports, it is clear that renal levels of CYP4A expression and excretion of 20-HETE are increased in kidney diseases. Thus, it is clear that inhibition of 20-HETE synthesizing enzymes would be beneficial for the treatment of kidney diseases.

Cerebrovascular diseases:

20-HETE is a potent vasoconstrictor eicosanoid which is produced from arachidonic acid by CYP4A isoforms in rat (Gebremedhin et al., Circ. Res. 87:60-65, 2000) and cat cerebral artery (Gebremedhin et al., J. Physiol., 507:771-781, 1998). Vasoconstriction of a cerebral artery causes reduction of cerebral blood flow. Decreases in cerebral blood flow were often observed

in cerebral diseases such as subarachnoid hemorrhage (Kehl et al., Am. J. Physiol. 282: H1556-1565, 2002), stroke, traumatic brain injury, dementia and Alzheimer diseases. Reduced cerebroarterial vasoconstriction mediated through the inhibition of 20-HETE formation can improve the reduced cerebral blood flow observed in the above-mentioned cerebral diseases. From the above-mentioned reports, an inhibitor of 20-HETE synthesis is considered to be a good therapeutic drug for subarachnoid hemorrhage, stroke, traumatic brain injury, dementia and Alzheimer diseases associated with decrease in cerebral blood flow.

Cardiovascular diseases:

Hypertension - Renal production of 20-HETE was increased in deoxycorticosterone acetate (DOCA)-salt hypertensive rats (Oyekan et al., Am. J. Physiol. 273: R293-R300, 1997; Oyekan et al., Am. J. Physiol. 276: R766-R755, 1999). Aminobenzotriazol, an inhibitor of 20-HETE synthesis prevented the development of hypertension in DOCA-salt hypertensive rats (Oyekan et al., Am. J. Physio. 276: R766-R755, 1999). These studies indicate that 20-HETE contributes to the development of DOCA-salt hypertension. Angiotensin H stimulates the formation of 20-HETE in the renal circulation of the rat (Croft et al., Am. J. Physiol. 279: F544-F551, 2000) and in the isolated perfused kidney (Carroll et al., Am. J. Physiol. 271: R863-R869, 1996). Blockade of the synthesis of 20-HETE attenuates the vasoconstrictor actions of angiotensin II in isolated renal arteries *in vitro* and the pressure response to intravenous infusion of angiotensin II in rats *in vivo* (Alonso-Galicia et al., Am. J. Physiol. 283:R60-68, 2002). These results suggest that elevations in the vascular production of 20-HETE may contribute to the development of angiotensin II-induced hypertension. Since an inhibitor of angiotensin converting enzyme inhibitor, and an angiotensin II receptor antagonist are good anti-

hypertensive drugs for essential hypertension in human, an inhibitor of 20-HETE synthesis is also considered to be a good anti-hypertensive drug for use in human hypertensive patients.

Heart diseases - 20-HETE is a potent constrictor of small blood vessels and has been suggested to play a crucial role in the generation of myogenic tone and the development of hypertension. Recently, Randriamboavonjy et al. (Randriamboavonjy et al., Hypertension 41:801-806, 2003) have confirmed that 20-HETE can cause vasoconstriction in isolated porcine coronary artery. These results indicate that the production of 20-HETE may contribute the pathophysiological states of angina pectoris and myocardial infarction. Inhibition of the production of 20-HETE would be beneficial to the above mentioned ischemic coronary heart diseases by inhibiting the coronary arterial vasoconstriction.

As can be seen from this discussion, it would be readily understood in the art which kidney diseases, which cerebrovascular diseases and which circulatory diseases could be treated using the compound of the instant application. It is clear that while the cited diseases are different, each of them has an underlying cause that is related to the production of 20-HETE. It is clear that the inhibition of 20-HETE synthesis using the compounds of the present application would be useful in the treatment of each of the diseases.

In view of these comments, Applicants assert that the claims are definite as written, and therefore respectfully request reconsideration and withdrawal of this rejection.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the

Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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